BIOGRAPHICAL SKETCH

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NAME: Shin Yajima

eRA COMMONS USER NAME (credential, e.g., agency login): SYAJIMA

POSITION TITLE: Postdoctoral Research Fellow

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Shimane University Medical School, Shimane, Japan	M.D.	03/2007	Medical Doctor
Osaka National Hospital, Osaka, Japan	Residency	03/2009	General and Thoracic Surgery
Osaka University, Osaka, Japan	Ph.D.	09/2018	Cardiovascular Surgery
Stanford University, Stanford, CA	Postdoctoral Fellow	Present	Cardiothoracic Surgery

A. Personal Statement

Throughout my clinical research, I found that insufficient myocardial revascularization had little impact on myocardial functional recovery since coronary artery bypass grafting (CABG) could approach and supply blood flow to the superficial coronary arteries, but not to intramyocardial microvascular arteries, particularly where microvasculature was either scarce or absent. During my Ph.D. in cardiovascular surgery, I focused on a prostacyclin analog that has thromboxane A2 synthase inhibitory activity and can promote angiogenesis and restore myocardial blood flow through proangiogenic and vasodilatory effects. I applied a microform of this compound in the porcine ischemia cardiomyopathy model with a direct epicardial placement, elucidating promoted myocardial angiogenesis, leading to myocardial function recovery. Then, I developed nanoparticles (NPs) that incorporated this compound which I subsequently applied to a rat ischemia myocardial reperfusion model with an intravenous injection to elucidate attenuated myocardial ischemia-reperfusion (I/R) injury. Furthermore, I have worked on tissue engineering for myocardial regeneration using induced pluripotent stem cells (iPSCs). With human iPSCs-derived cardiomyocyte sheets of direct implantation on the ischemic myocardial tissue, we elucidated myocardial regeneration through proangiogenic effects, improved cardiac performance, and attenuated left ventricular remodeling in both small and large animals. These works have already been published (below are representative), and I gained several academic awards and research grants (ongoing research support; Japan Heart Foundation/Bayer Research Grant Abroad, 01/01/2022-12/31/2022). My career goal is to become a leader in academic cardiothoracic surgery. During my postdoctoral fellowship, I plan to develop novel therapeutic methods to obtain better outcomes for ischemic heart disease through engineering analysis and the creation of innovative solutions. I am extremely excited to start on the proposed project, as it perfectly intertwines my bioengineering background and clinical interests. As such, the School of Medicine Dean's Postdoctoral Fellowship will be invaluable to my development as a young investigator. Dr. Woo is an exceptional mentor with remarkable renown for training academic surgeons and Stanford University provides incredible resources for research. I feel extremely fortunate to have such an ideal environment to carry out this project and continue advancing the field of cardiothoracic surgery.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022-present	Postdoctoral Fellow, Department of Cardiothoracic Surgery, Stanford University School of Medicine, Stanford, CA Supervisor: Y. Joseph Woo, MD
2020 - 2022	Assistant Professor, Department of Cardiovascular Surgery, Hyogo College of Medicine, Hyogo, Japan
2019 - 2020	Staff of Cardiovascular Surgery, Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan
2018 - 2019	Chief of Cardiovascular Surgery, Department of Cardiovascular Surgery, Japan Community Healthcare Organization Osaka Hospital, Osaka, Japan
2013 - 2018	Graduate Student, Academic Fellow, Osaka University Graduate School of Medicine , Osaka, Japan Supervisor: Yoshiki Sawa, MD, PhD
2011 - 2013	Staff of Cardiovascular Surgery, Department of Cardiovascular Surgery, East Takarazuka Satoh Hospital, Hyogo, Japan
2009 - 2011	Residency of Cardiovascular Surgery, Department of Cardiovascular Surgery, Osaka National Hospital, Osaka, Japan
2007 - 2009	Residency of Surgery, Department of Cardiovascular Surgery, Osaka National Hospital, Osaka, Japan

Honors

2019	**Best Scientific Paper**, The Japanese Association for Thoracic Surgery, Japan
2019	**Japan Heart Foundation/Bayer Research Grant Abroad**, Japan
2019	**Best Teaching Award**, National Cerebral, and Cardiovascular Center, Japan
2019	**Young Investigator's Award**, Department of Surgery, Osaka University Graduate School of Medicine, Japan
2018	**Best of Basic Scientific Research for Cardiovascular Surgery,** Japan Circulation Society, Japan
2018	**Young Investigator's Award**, Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Japan
2017	**Young Investigator Award**, The 60th Annual Meeting of Kansai Thoracic Surgical Association, Japan
2016	**Best of Basic Scientific Poster**, American Heart Association
2016	**Basic Research Award (Hearse-Yamamoto Award)**, 46th congress of the Japanese Society for Cardiovascular Surgery, Japan
2016	**Young Investigator Award**, The 16th Annual Congress of the Japanese Surgical Society, Japan
2016	**Young Investigator Award**, The 59th Annual Meeting of Kansai Thoracic Surgical Association, Japan

C. Contributions to Science

I. Understanding the importance of the myocardial regeneration

In my early clinical carrier as a cardiothoracic surgeon, I realized that a certain number of patients with ischemic heart disease did not recover after undergoing CABG. Through clinical research, I discovered that approximately half of the patients with ischemia cardiomyopathy did not exhibit myocardial recovery after CABG; rather, they showed a significantly higher rate of readmission due to heart failure. To be more detailed, extended myocardial remodeling of the heart or previous multiple coronary stenting negatively affected the myocardial functional recovery. Coronary stents can cause physical side-branch obstructions or occlusions due to multiple contiguous and overlapping stents, leading to a compromised collateral blood flow and a greater resultant extent of myocardial ischemia and necrosis. This led us to the conclusion that a greater amount of less viable myocardium or myocardial microvascular dysfunction may hinder myocardial recovery (1).

1. **Yajima S**, Yoshioka D, Fukushima S, Toda K, Miyagawa S, Yoshikawa Y, Hata H, Saito S, Domae K, Sawa Y. Multiple coronary stenting negatively affects myocardial recovery after coronary bypass grafting. Gen Thorac Cardiovasc Surg. 2018 Aug;66(8):446-455. PMID: 29761271.

II. Developing a novel prostacyclin analog to induce angiogenesis for ischemia heart disease model

During my Ph.D., I explored how myocardial infarction (MI) led to left ventricle remodeling due to progressive microvasculature dysfunction in which irreversible impairment in microvascular function had been extended from the infarcted region into the infarct-border or remote regions using a porcine chronic MI model (2). This suggested that additional treatments to stabilize or enhance the microvascular function in a border area would contribute to improved outcomes. We developed a novel slow-releasing form of prostacyclin analog with inhibitory activity of thromboxane A2 synthase that could strengthen the pathway toward the production of prostacyclin, thus contributing to robust angiogenesis. Using this novel compound, I applied this method to a porcine ischemia cardiomyopathy model with a direct epicardial replacement on the ischemic myocardium, resulting in the myocardial blood flow significantly increasing in the peri-infarct area; this finding aligned with the significantly increased capillary density with up-regulated angiogenic cytokine expression. Furthermore, I combined a pedicled omental flap with this compound and demonstrated that the omentum extended prominent functional collateral arteries to the myocardial ischemic border area associated with significantly improved cardiac functional recovery (3). Then, I created pegylated stealth liposomal NPs that incorporated this compound with improved stability and prolonged circulation time. With these NPs, I applied a rat I/R model with an intravenous injection to elucidate the specific accumulation of NPs in the ischemic myocardium associated with smaller infarct size, better-preserved capillary networks, and a better-preserved myocardial blood flow via up-regulated proangiogenic cytokines and down-regulated inflammatory cytokines (4). Hence, I helped develop the novel compound and contributed to the treatment of microvascular dysfunction.

2. **Yajima S**, Miyagawa S, Fukushima S, Isohashi K, Watabe T, Ikeda H, Horitsugi G, Harada A, Sakaniwa R, Hatazawa J, Sawa Y. Microvascular Dysfunction Related to Progressive Left Ventricular Remodeling due to Chronic Occlusion of the Left Anterior Descending Artery in an Adult Porcine Heart. Int Heart J. 2019 May 30;60(3):715-727. PMID: 31105143.
3. **Yajima S**, Miyagawa S, Fukushima S, Sakai Y, Isohashi K, Watabe T, Ikeda H, Horitsugi G, Harada A, Sakaniwa R, Hatazawa J, Sawa Y. A prostacyclin agonist and an omental flap increased myocardial blood flow in a porcine chronic ischemia model. J Thorac Cardiovasc Surg. 2018 Jul;156(1):229-241.e14. PMID: 29627179.
4. **Yajima S**, Miyagawa S, Fukushima S, Sakai Y, Iseoka H, Harada A, Isohashi K, Horitsugi G, Mori Y, Shiozaki M, Ohkawara H, Sakaniwa R, Hatazawa J, Yoshioka Y, Sawa Y. Prostacyclin Analogue-Loaded Nanoparticles Attenuate Myocardial Ischemia/Reperfusion Injury in Rats. JACC Basic Transl Sci. 2019 Jun;4(3):318-331. PMID: 31312756

III. Tissue-engineered iPSCs cell sheet biology to myocardial regeneration

We have created tissue-engineered cell sheets derived from these stem cells and applied them to various ischemic heart disease models. In terms of iPSCs, we generated engineered cardiac tissue with human iPSCs-derived cardiomyocytes that contained different ratios (25%, 50%, 70%, or 90%), and elucidated engineered cardiac tissues containing 50–70% cardiomyocytes formed stable structures and produced enhanced electrical and mechanical functions, thus increasing the overall cardiotherapeutic potential in the rat chronic MI model (5). In addition, we created organized and functional cardiac tissue-like constructs to demonstrate that multilayered elongated human iPSCs-derived cardiomyocytes within the constructs showed upregulated gene expression of cardiac markers, enhanced extracellular recording, and robust drug response. In addition, we demonstrated post-surgery cell survival in cardiac tissue-like constructs and their ability to repair MI in a rat model (6). For clinical application, we have also worked on detecting residual undifferentiated human induced iPSCs and malignantly transformed cells that may lead to tumor formation and we have developed a highly sensitive tumorigenicity assay that combines the *in vitro quantification* of tumorigenic cells and *in vivo* tumorigenicity assessment to verify the safety of human-induced iPSC-derived cardiomyocytes for regenerative therapy in heart failure or heart disease (7). Furthermore, we developed a novel spray method that can be efficiently spread over the surface of the heart in fibrinogen and thrombin solutions and showed the efficacy of the allogeneic adipose-derived mesenchymal stem cells that contained abundant angiogenic and cardioprotective cytokines on porcine ischemic cardiomyopathy model with functional cardiac recovery (8).

5. Iseoka H, Miyagawa S, Fukushima S, Saito A, Masuda S, **Yajima S**, Ito E, Sougawa N, Takeda M, Harada A, Lee JK, Sawa Y. Pivotal Role of Non-cardiomyocytes in Electromechanical and Therapeutic Potential of Induced Pluripotent Stem Cell-Derived Engineered Cardiac Tissue. Tissue Eng Part A. 2018 Feb;24(3-4):287-300. PMID: 28498040

6. Li J, Minami I, Shiozaki M, Yu L**, Yajima S**, Miyagawa S, Shiba Y, Morone N, Fukushima S, Yoshioka M, Li S, Qiao J, Li X, Wang L, Kotera H, Nakatsuji N, Sawa Y, Chen Y, Liu L. Human Pluripotent Stem Cell-Derived Cardiac Tissue-like Constructs for Repairing the Infarcted Myocardium. Stem Cell Reports. 2017 Nov 14;9(5):1546-1559. PMID: 29107590
7. Ito E, Miyagawa S, Takeda M, Kawamura A, Harada A, Iseoka H, **Yajima S**, Sougawa N, Mochizuki-Oda N, Yasuda S, Sato Y, Sawa Y. Tumorigenicity assay essential for facilitating safety studies of hiPSC-derived cardiomyocytes for clinical application. Sci Rep. 2019 Feb 13;9(1):1881. PMID: 30760836
8. Mori D, Miyagawa S, **Yajima S**, Saito S, Fukushima S, Ueno T, Toda K, Kawai K, Kurata H, Nishida H, Isohashi K, Hatazawa J, Sawa Y. Cell Spray Transplantation of Adipose-derived Mesenchymal Stem Cell Recovers Ischemic Cardiomyopathy in a Porcine Model. Transplantation. 2018 Dec;102(12):2012-2024. PMID: 30048399

IV. Other scientific contributions of clinical research focusing on heart failure

Throughout my entire clinical carrier, we have performed several clinical studies on valvular heart disease and end-stage heart failure. Regarding valvular heart diseases, we demonstrated the risk factors for heart remodeling after aortic valve replacement in patients with chronic aortic insufficiency and offered the optimal surgical timing (9). We clarified the results of redo mitral valve replacement, where the mitral paravalvular leakage frequently occurred and a risk factor for operative mortality (10). We detected the predictive factors for recurrent significant tricuspid regurgitation that lead to right heart failure after aortic valve replacement (11). Regarding end-stage heart failure, we determined the optimal indication and selection of the central extracorporeal life support, suggesting a promising method to promptly establish sufficient flow support for heart and lung unloading in patients with refractory congestive heart failure (12).

9. Koga-Ikuta A, Fukushima S, Kawamoto N, Saito T, Shimahara Y, **Yajima S**, Tadokoro N, Kakuta T, Fukui T, Fujita T. Reverse remodeling after aortic valve replacement for chronic aortic regurgitation. Interact Cardiovasc Thorac Surg. 2021 Jun 28;33(1):10-18. PMID: 33615334
10. **Yajima S**, Fukushima S, Yamashita K, Shimahara Y, Tadokoro N, Kakuta T, Sakaniwa R, Kobayashi J, Fujita T. Long-term outcomes after reoperation for mitral paravalvular leaks: a single-centre experience. Eur J Cardiothorac Surg. 2020 Sep 18. PMID: 32944776.
11. **Yajima S**, Yoshioka D, Toda K, Fukushima S, Miyagawa S, Yoshikawa Y, Saito S, Domae K, Ueno T, Kuratani T, Sawa Y. Definitive Determinant of Late Significant Tricuspid Regurgitation After Aortic Valve Replacement. Circ J. 2018 Feb 23;82(3):886-894. PMID: 29238013.
12. Fukushima S, Tadokoro N, Koga A, Shimahara Y, **Yajima S**, Kakuta T, Kuroda K, Nakajima S, Watanabe T, Yanase M, Fukushima N, Kobayashi J, Fujita T. Central conversion from peripheral extracorporeal life support for patients with refractory congestive heart failure. J Artif Organs. 2020 Sep;23(3):214-224. PMID: 32076901.

Complete List of Published Work in My Bibliography:

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